# OVERVIEW OF CHLORPROPHAM RISK ASSESSMENT

## Introduction

This document summarizes EPA's human health and drinking water risk findings and conclusions for the herbicidal carbamate pesticide chlorpropham, as presented fully in the documents, "Chlorpropham HED Revised Human Health Risk Assessment Chapter for the Tolerance Reassessment Eligibility Decision, June 7, 2002" and "Revised FQPA Drinking Water Assessment for Chlorpropham, June 5, 2002". The purpose of this overview is to assist the reader by identifying the key features and findings of these risk assessments. This overview was developed in response to comments and requests from the public, which indicated that the risk assessments were difficult to understand, that they were too lengthy, and that it was not easy to compare the assessments for different chemicals due to the use of different formats.

The chlorpropham risk assessment, and additional supporting documents, are posted on EPA's Internet website (http://www.epa.gov/pesticides/chlorpropham.html) and are available in the Pesticide Docket for public viewing. The availability of the Agency's report on the FQPA Tolerance Reassessment Decision (TRED) for chlorpropham will be announced in a Federal Register Notice. Prior to publication of the Notice, the Agency conducted a closure conference call to describe the regulatory decisions to stakeholders.

The Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Food Quality Protection Act (FQPA) of 1996, requires EPA to review all the tolerances for registered chemicals in effect on or before the date of the enactment of FQPA. In reviewing these tolerances, the Agency must consider, among other things, aggregate risks from non-occupational sources of pesticide exposure, whether there is increased susceptibility to infants and children, and the cumulative effects of pesticides with a common mechanism of toxicity. The tolerances are considered reassessed once the safety finding has been made or a revocation occurs. A reregistration eligibility decision (RED) for chlorpropham was finalized and signed on August 1, 1996, prior to FQPA enactment; therefore, tolerances needed to be reassessed to reflect the provisions of FQPA.

Risks summarized in this document are those that result only from the use of chlorpropham. The FQPA requires that the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity". The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. The Agency did not perform a cumulative risk assessment as part of this tolerance reassessment of chlorpropham because the Agency has determined that chlorpropham does not share a common mechanism of toxicity with other cholinesterase-inhibiting methyl-carbamates.

## Use Profile

**Herbicide:** registered for use on the following crops/sites: sprout control on post-harvest stored potatoes. There are four Special Local Needs [24(c)] registrations. They are for use on Easter lilies (on approximately 150 acres annually in Oregon and California), on gingko trees in Washington, DC, and on post-harvest stored potatoes growing in high humidity conditions in the state of Maine which requires a higher application rate.

**Formulations:** registered formulations include a technical grade (from 98%, to 99% active ingredient (a.i.)), aerosol ready-to-use (RTU) (from 46.5 to 98.7% a.i.), and liquid emulsifiable concentrate (EC), (from 23.8 to 36% a.i.). The registrant of an additional RTU product (formulated at 49.65% a.i.) has requested a voluntary cancellation of this product.

**Methods of Application:** may be applied by direct spray, low volume direct spray (concentrate), high pressure spray (dilute), stored commodity fumigation, and stored commodity non-fumigation (aerosol).

**Application Rate:** chlorpropham application rates to post-harvest potatoes vary, and depend on method of application, length of storage, and storage temperature. Rates of application to post-harvest potatoes destined for processing range from a maximum total application rate of 1.65 lb a.i./600 hundred weight (cwt) to 1.65 lb a.i./400 cwt. Post-harvest stored potatoes destined for fresh markets may receive a maximum total application rate of 1.45 lb a.i./600 cwt. Current labels do not restrict or limit the number of applications to stored potatoes, as long as the maximum application rate is not exceeded. A total of approximately 300 lbs of chlorpropham a.i is used annually on gingko trees in Washington, DC, at an application rate of 0.02 lbs a.i./gallon. The maximum total application rate for the Easter lily bulb use is 3.99 lb a.i./A.

**Application Timing:** chlorpropham may be applied pre-bloom (for Easter lilies and gingko trees), and as a dormant application to post-harvest potatoes in storage. Post-harvest potatoes are the only food/feed use.

**Annual Poundage:** the best available data for total annual amount of chlorpropham active ingredient (a.i.) used is from a USDA National Agricultural Statistics Service (NASS) publication for 1996. Total annual chlorpropham used was approximately 445,600 pounds.

**Registrants:** Aceto Agriculture Chemicals Corporation, Cerexagri, Inc., and Pin/Nip Inc.

## Human Health Risk Assessment

***Acute Dietary (Food) Risk***

Acute dietary risk from food is calculated by considering what is eaten in one day. A risk estimate that is less than 100% of the acute Population Adjusted Dose (aPAD) (the dose at which an individual could be exposed on any given day and no adverse health effects would be expected) is not of concern to the Agency. The aPAD is the reference dose (RfD) adjusted for the FQPA Safety Factor.

The Agency performed a conservative deterministic (Tier 1) analysis (which assumed tolerance level residues based on existing and/or reassessed tolerances and 100 % crop treated (CT). The acute dietary exposure analysis is based on the Dietary Exposure Evaluation Model (DEEM™). One day consumption data from USDA's Continuing Surveys of Food Intake by Individuals (CSFII 1989-92) are used on an individual-by-individual basis for acute exposure assessment.

- Acute dietary (food) risk is not of concern (4.0% of the aPAD) at the 95$^{th}$ exposure percentile for females 13-50 years old (the only subgroup requiring an acute assessment).

- An acute endpoint for the general population, including infants and children, was not available from the toxicity studies, including the developmental toxicity studies. The maternal toxicity in these studies was not attributable to a single exposure. Therefore, no toxicity endpoint or dose was selected for the general population including infants and children.

- The toxicity endpoint for the acute dietary assessment is increased resorption and post-implantation loss based on a developmental toxicity study in rabbits (NOAEL = 250 mg/kg/day). These effects were observed at 500 mg/kg/day (LOAEL).

- The uncertainty factor is 100x, 10x for intraspecies variability and 10x for interspecies extrapolation.

- The FQPA Safety Factor was reduced to 1X for acute and chronic exposures because: 1) the toxicology data base is complete; 2) there is no indication of increased susceptibility of rats or rabbit fetuses to *in utero* and/or postnatal exposure in the developmental and reproductive toxicity studies; 3) a developmental neurotoxicity study is not required; 4) dietary (food) exposure estimates are partially refined resulting in a more realistic estimate of dietary exposure; 5) quantifiable contamination of surface or ground water is not likely to result from this use; and 6) there are currently no registered residential uses of chlorpropham, therefore, this type of exposure to infants and children is not expected.

- The acute RfD (aRfD) is 2.5 mg/kg/day. Because the FQPA Safety Factor was reduced to

1X, the aPAD is equal to the aRfD.

- There is no evidence of endocrine disruption from exposure to chlorpropham.

***Chronic Dietary (Food) Risk***

Chronic dietary risk from food is calculated by using the average consumption values for food and average residue values for those foods over a lifetime. Chronic dietary exposure that is less than 100% of the chronic Population Adjusted Dose (cPAD) does not exceed the Agency's level of concern. The cPAD is the chronic reference dose (cRfD) adjusted for the FQPA Safety Factor.

Residues of chlorpropham *per se* from USDA Pesticide Data Program (PDP) monitoring data, calculated as point estimates, were used for potatoes in the chronic dietary assessment. Anticipated residues of parent chlorpropham and the 4-HSA metabolite in livestock tissues were derived from the ruminant feeding studies and were used as point estimates in the assessment. Total residues of chlorpropham and the metabolite 4-HSA in milk were calculated by determining the ratio of residues of parent to metabolite in milk from the feeding study and applied to the amount of parent reported in milk in the PDP monitoring data.

- Chronic dietary risk estimates for food are below the Agency's level of concern (<100% cPAD) for the general U.S. population (4% of the cPAD) and all population subgroups. The chronic dietary exposure estimate for highest exposed population subgroup, children 1-6 years old, is 10% of the cPAD.

- The toxicity endpoint for the chronic dietary risk assessment is thyroid toxicity, based on the results of a 2-year feeding study in dogs, where increased thyroid weights and histopathological changes in the thyroid were observed (NOAEL=5 mg/kg/day). These effects were observed at 50 mg/kg/day (LOAEL).

- The uncertainty factor is 100x; 10x for intraspecies variability and 10x for interspecies extrapolation.

- The chronic RfD (cRfD) is 0.05 mg/kg/day. As noted in the Acute Dietary Risk section, the FQPA Safety Factor was reduced to 1x.

***Cancer Dietary (food) Risk***

The Agency has classified parent chlorpropham as a "Group E" human carcinogen (no evidence of carcinogenicity). However, some chlorpropham is metabolized to 3-chloroaniline (3-CA) in potatoes and some anilines are known carcinogens. The Agency does not have data on 3-CA necessary to conduct a carcinogenicity risk assessment. However, data are available for 4-chloroaniline (4-CA) which is structurally similar to 3-CA and has a cancer potency factor ($Q_1$*) of $1.12 \times 10^{-1}$ $(mg/kg/day)^{-1}$. This $Q_1$* was used as a surrogate to assess the potential cancer risk from 3-CA. However, the use of the 4-CA carcinogenic potency is expected to overestimate risk.

- In livestock metabolism studies, 3-CA was *not detected* in milk, meat, kidney or fat. 3-CA was detected in liver. Although no 3-CA was detected in milk, a cancer dietary exposure assessment was performed using ½ LOD (limit of detection) for milk as well as the 3-CA residue found in liver and potatoes. This exposure scenario reflects a conservative assumption that finite residues may be expected in milk and liver consumed by individuals living in a "local milkshed" where cattle may be fed processed potato waste from nearby potato processing plants. The cancer dietary risk estimate for the general population is $3.4 \times 10^{-6}$, based on this conservative "local milkshed" scenario.

- A second cancer dietary exposure assessment was performed using estimated potato residues only and omitting milk and cattle liver. This assessment reflects an exposure scenario that assumes no potato waste containing chlorpropham is fed to livestock. This typical scenario is more realistic than the local milkshed scenario since residues of 3-CA are not expected in milk and only a small amount of the population can be assumed to live in an area where local potato waste may be fed to livestock. The cancer dietary risk estimate for the typical scenario is $2.2 \times 10^{-6}$.

The Agency's level of concern for lifetime cancer risk is generally $1.0 \times 10^{-6}$. However, for chlorpropham, several factors are expected to contribute to overestimating risk including use of the surrogate $Q_1$*, the 10-fold range between the NOAEL and LOAEL derived from the 2 year dog feeding study, and the conservatism associated with the use of anticipated residues. Therefore, the Agency does not consider the dietary cancer risk estimate from chlorpropham use to be of concern.

***Drinking Water Dietary Risk***

Drinking water exposure to pesticides can occur through surface and/or ground water contamination. EPA considers acute (one day) and chronic (lifetime) drinking water risks and uses either modeling or actual monitoring data, if available, to estimate those risks. To determine the maximum allowable contribution from water allowed in the diet, EPA looks at how much of the overall allowable risk is contributed by food, then calculates a "drinking water level of comparison" (DWLOC) to determine whether modeled or monitoring levels exceed this level.

The Agency uses a DWLOC as a surrogate to capture risk associated with exposure from pesticides in drinking water. The DWLOCs represent the maximum contribution to the human diet that may be attributed to residues of a pesticide in drinking water after dietary exposure is considered. Risks from drinking water are assessed by comparing the DWLOCs to the estimated environmental concentrations (EECs) in surface and/or ground water. When the EECs are less than the DWLOCs, the Agency is not concerned with drinking water risks.

As previously noted, annual outdoor use of chlorpropham is limited to 300 lbs a.i. each on Easter lilies and gingko trees. However, accurate assessment of the drinking water contamination potential posed by these limited outdoor uses of chlorpropham and its 3-chloroaniline metabolite, is hampered by the near complete lack of environmental fate data for both compounds. Therefore, the Agency is relying on modeling to estimate drinking water dietary risks and on monitoring data for other pesticides used in the lily bulb growing region along with fate parameters from surrogate

chemicals to characterize exposures.

Gingko Tree Use – Surface and Ground Water

Chlorpropham is applied to gingko trees in Washington, DC by mist blower to "near dripping point" at an application rate of 0.02 lbs a.i./gallon. There are no drinking water intakes on the Potomac River downstream of Washington, DC, so there is no potential for exposure to chlorpropham through drinking water. Therefore, neither surface water or ground water sources of drinking water are of concern as a result of the gingko tree use.

Easter Lilies – Surface Water

The only chlorpropham use that may result in exposure through drinking water is application to Easter lilies. The Agency assessed potential exposure to water based on the Easter lily use which is limited to Curry County, Oregon and Del Norte County, California. Approximately 150 acres (1/4 square mile) receives treatment with chlorpropham annually. Any potential exposure would be limited to these two counties. Surface water intakes are not located near lily bulb cultivating areas, therefore, the potential for exposure to CIPC/3-CA in surface water sources of drinking water is negligible. The Agency concludes that no population group is exposed to chlorpropham residues in surface water sources of drinking water at a level that poses an acute or chronic risk concern.

Easter Lilies – Ground Water

Estimated drinking water concentrations for ground water are based on the SCI-GROW model. The model is a conservative, Tier I assessment that provides a reasonable estimate of exposure in hydrologic environments similar to those in which lily bulbs are grown. However, the modeled EEC is a conservative estimate of lifetime exposure and does have considerable uncertainty because of the lack of environmental fate data.

- For acute risk, potential exposure to chlorpropham from drinking water is not of concern. The acute ground water EEC for chlorpropham of 100 ppb does not exceed the DWLOC (72,000 ppb).

- For chronic risk, the Easter lily use is not of concern. The modeled EEC is 100 ppb which does not exceed the 450 ppb DWLOC for kids 1-6 years (the most sensitive subpopulation).

- For carcinogenic risk, potential chronic exposure to chlorpropham from ground water sources of drinking water associated with the Easter lily bulb use is estimated to range from 2.0 ppb to 8.0 ppb. This range is based on varying modeling parameters including degradation half life and assuming 100% of the parent chlorpropham is degraded to 3-chloroanaline. As such, these estimates may not be suitable for a cancer assessment and will overestimate cancer risk.

***Residential Risk***

There are currently no registered residential uses of chlorpropham. Therefore, there is no expected exposure of homeowners to chlorpropham and aggregation with dietary sources of exposure is not necessary.

***Aggregate Risk***

The aggregate risk assessment considers exposure through food, drinking water, and non-occupational uses (i.e., residential use). Since there are no chlorpropham residential uses, the aggregate assessment examines the combined exposure through food and drinking water only.

- Acute aggregate risk estimates from exposure to chlorpropham in food and water do not exceed the Agency's level of concern. The modeled groundwater EEC does not exceed the acute DWLOC for females 13-50 years old nor is there potential acute exposure to chlorpropham from surface water sources that exceed the Agency's level of concern.

- Chronic aggregate risk estimates from exposure to chlorpropham in food and water do not exceed the Agency's level of concern. The modeled groundwater EEC does not exceed the chronic DWLOC for the US population and all population subgroups nor is there potential chronic exposure to chlorpropham from surface water sources that exceed the Agency's level of concern.

***Aggregate Cancer Risk***

The carcinogenic risk estimate ($2.2x10^{-6}$) for dietary (food) exposure based on the typical use scenario fills the "risk cup". The only potential drinking water concern is for ground water associated with the use on Easter lilies in Oregon and California (surface water is not of concern for any use). However, the cancer risk assessment is based on a surrogate $Q_1$* which is likely to overestimate cancer risk. Similarly, the modeled ground water EEC reflects a bounding analysis which would not appreciately contribute to aggregate risks at the low end but would represent a risk concern based on worse case assumptions. These uncertainties which likely overestimate exposure and risk, combined with the limited use area and reduction in the maximum application rate (50%), give the Agency reasonable assurance that aggregate cancer risks are not of concern.

***Occupational Risk***

Chlorpropham is currently under review for tolerance reassessment only. Occupational risk management decisions were made as part of the 1996 Chlorpropham RED, and no new data has been received to warrant reconsideration of these risks. Therefore, no occupational risk assessment was conducted.

## Ecological Risk

Chlorpropham is currently under review for tolerance reassessment only. Ecological risk management decisions were made as part of the 1996 Chlorpropham RED, and no new data has been received to warrant reconsideration of these risks. Therefore, an ecological risk assessment was not conducted.

## Summary of Pending Data

- All product chemistry data requirements have been fulfilled for 1. Aceto 98% T (EPA Reg. No. 2749-102, 2. Cerexagri 99% T (EPA Reg. No. 2792-67), and 3.Pin Nip 98% T (EPA Reg. No. 65726-2) except data are required concerning UV/Visible Absorption (OPPTS 830.7050).

- The requirements for Analytical Methodology (OPPTS 860.1340) will remain unfulfilled until receipt of the revised version of the proposed GC/NPD method for tolerance enforcement in stored potato commodities.

- Method validation for HPLC/UV method for tolerance enforcement in stored potato commodities will remain unfulfilled for the registrant (Pin Nip, Inc) until successful radiovalidation, confirmatory method, and independent laboratory validation have been submitted and reviewed.

- Separate enforcement methods (GC/MSD for chlorpropham and HPLC for 4-HSA) have been submitted for determination of chlorpropham and its 4-HSA metabolite in meat and milk. Method validation for tolerance enforcement will remain unfulfilled until successful ILVs are submitted.

**Additional Generic Data Requirements**

- A special residue study (under crop field trial guideline study number OPPTS 860.1500) is required to determine the potential for chlorpropham degradates to form and possibly deposit as residues in or on stored potatoes during application as a result of thermal degradation. The study is required because the Agency cannot determine whether or not the chlorophenyl isocyanate, or other thermal degradates, are produced during aerosol treatment (based on the literature citations and the submitted metabolism study alone). The study should include the range of temperatures typically used by the generators, at what temperature the decomposition products are formed during the process, and the presence and amount of any isocyanates (in particular, chlorophenyl isoncyanate, and 5-chloro-2-benzoxazolinone).

- The protocol for this study must be submitted to the Agency prior to initiating the study. A residue analytical method may need to be developed, should existing methodology be insufficient. Technical registrants will be sent a Federal Insecticide, Fungicide, Rodenticide Act (FIFRA) Section 3(c)(2)(B) Data-Call-In (DCI) letter in a separate mailing.